PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 889 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/014359	International filing date *(day/month/year)* 16.12.2004	Priority date *(day/month/year)* 19.12.2003

International Patent Classification (IPC) or national classification and IPC
INV. A61K31/198 A61K31/225 A61K31/185 A61K31/385 A61K31/07 A61K31/375 A61K31/355 A61P13/12 A61P39/06

Applicant
BIO 3 RESEARCH SRL

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand 14.10.2005	Date of completion of this report 05.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Cielen, E Telephone No. +31 70 340-4540

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/014359

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3(a) and 23.1(b))
   ☐ publication of the international application (under Rule 12.4(a))
   ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-5 as originally filed

Claims, Numbers

1-8 received on 14.10.2005 with letter of 14.10.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☒ the claims, Nos. 9
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6-8

   because:

   ☒ the said international application, or the said claims Nos. 6-8, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination *(specify)*:

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

   ☐ no international search report has been established for the said claims Nos.

   ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

   ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

   ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

   ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

   ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-8
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 14.10.2005 are in accordance with Article 34(2)(b) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 6-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Present claims 6-8 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D1: US-A-4 794 124 (YAMAMOTO ET AL) 27 December 1988 (1988-12-27)
D2: US-A-4 849 452 (DULCE ET AL) 18 July 1989 (1989-07-18)
D3: WO 93/14750 A (THE ROCKEFELLER UNIVERSITY; ALTEON INC) 5 August 1993 (1993-08-05)
D4: US-A-5 607 974 (DROEGE ET AL) 4 March 1997 (1997-03-04)
D5: US-A-4 792 549 (TAKAHASHI ET AL) 20 December 1988 (1988-12-20)
D6: WO 02/34303 A (NITROMED, INC; TRUSTEES OF BOSTON UNIVERSITY; LOSCALZO, JOSEPH; VITA,) 2 May 2002 (2002-05-02)
D7: US 2002/137785 A1 (KINDNESS GEORGE ET AL) 26 September 2002 (2002-09-26)
D8: US-A-6 060 446 (ZALOGA ET AL) 9 May 2000 (2000-05-09)
D9: DATABASE WPI 6 September 1991 (1991-09-06), Derwent Publications Ltd., London, GB; Class 914,page 2, AN 1991-306713 XP002326744 FUNATO TOSHIAKI ET AL.: "Oral amino acid preparation for cardiac failure" & JP 03 204814 A (OTSUKA SEIYAKU KOGYO KK) 6 September 1991 (1991-09-06)
D10: DE 34 14 491 A1 (DIETL,HANS,DR) 24 October 1985 (1985-10-24)
D11: MOBERLY JAMES B ET AL: "Elevation of whole-body glutathione in peritoneal dialysis patients by L-2-Oxothiazolidine-4-carboxylate, a cysteine prodrug (Procysteine)" JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 9, no. 6, June 1998 (1998-06), pages 1093-1099, XP008046078 ISSN: 1046-6673
D12: US-B1-6 627 659 (SANTANGELO FRANCESCO) 30 September 2003 (2003-09-30)
D13: WO 00/53176 A (UNI-CI S.R.L; DALL'AGLIO, ROBERTO; BORGONOVO, MARGHERITA; INTROINI, CA) 14 September 2000 (2000-09-14)
D16: M. H. BEERS; R. BERKOW: "The Merck Manual of Diagnosis and Therapy, Seventeenth Edition" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION N.J. , XP002326823

The following document was cited by the Applicant:

D17: SANTANGELA F: "Intracellular thiol concentration modulating inflammatory response: Influence on the regulation of cell functions through cysteine

prodrug approach" CURRENT MEDICAL CHEMISTRY, vol. 10, 2003, pages 2599-2610.

V.iii. Article 33(2) PCT.

(a) The scope of claim 5 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any document disclosing a medical use of a composition suitable for oral administration comprising cysteine or cystine will be novelty-destroying for the subject-matter of claim 5.

(b) Claims 1-6 relate to the mechanism underlying the treatment of the claimed diseases with cystine and/or cysteine. However, the mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect. Even if the effect on oxidative stress by cystine and/or cysteine is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application, nor can it render the known treatment of a specified pathological condition, in the present case the known haemodialysis treatment of patients suffering from chronic kidney failure with cystine and/or cysteine, novel (see **V.iii(c)10** below). Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition.

Consequently, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compounds, it is only the therapeutic effect of the medicament, i.e. the use of cystine and/or cysteine in haemodialysis treatment of patients suffering from chronic kidney failure, which is relevant for the assessment of novelty and inventive step.

(c) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 is not new in the sense of Article 33(2) PCT:

1. Document D1 discloses the use of orally administered cysteine for the treatment of diabetic complications, such as nephropathy, which falls within the definition "acute or chronic

kidney diseases" (column 2, lines 25-54; column 6, lines 10-16). The daily dose ranges from 10-5000 mg, in single or divided dosages (column 3, lines 1-13). According to D16, diabetic nephropathy is a major cause of chronic renal failure and the most common cause of end-stage renal disease (Table 222-3; p. 1845, paragraph bridging left- and right-hand column); therefore, treatment of diabetic nephropathy *prevents* chronic kidney failure and end-stage renal disease.

It is recognised that the treatment of diabetic nephropathy by oral cysteine in D1 is not supported by data; however, the present application also provides a *mere statement* about the clinical efficacy of cysteine and/or cystine in the claimed diseases, without any pharmacological data. Therefore, the present description provides *no further evidence* showing the actual claimed effect of cysteine and/or cystine than did the prior art document D1. Accordingly, in the absence, in the patent application as originally filed, of any data providing additional technical information in relation to the actual treatment of the claimed kidney diseases by cysteine and/or cystine compared with the disclosure in the prior art document D1, it must be concluded that the subject-matter of the patent application is anticipated by the disclosure in D1. Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1, 3, 5 and 7-8 is not novel over D1.

2. Document D2 reports the use of L-cysteine in an amount of 0.75g/dose for the treatment of nephro-urological disorders, such as kidney stones, a disease which falls within the definition "acute or chronic kidney diseases" (column 2, lines 24-44; column 2, line 60 - column 3, line 11; claims). Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1, 3, and 5 is not novel over D2.

3.Document D3 teaches the use of an agent which inhibits the formation of advanced glycosylation end products of target proteins, such as cysteine, for the treatment of diabetic kidney disease or glomerulonephritis, which fall within the definition "acute or chronic kidney diseases" (p. 5, line 13 - p. 6, line 6; p. 6, lines 29-32; p. 7, lines 14-20; p. 17, lines 6-22); claims 1, 7, 15, 17, 18, 31). The compositions can be administered orally (claim 14). According to D16, glomerulonephritis is a major cause of acute renal failure (Table 222-1); therefore, treatment of glomerulonephritis *prevents* acute kidney failure.

Again, the fact that D3 contains no data supporting the actual treatment of diabetic kidney disease or glomerulonephritis by oral cysteine cannot render the present claims novel over D3, as data are also lacking in the present application (see also item **V.iii(c)(1)**). Moreover, each feature (cysteine, oral administration, diabetic kidney disease) is claimed separately as a preferred embodiment. Therefore, and in view of item **V.iii(a)**, the subject-

matter of present claims 1 and 5 is not novel over D3.

4. The subject-matter of the present application can be regarded as a selection invention over D4, which therefore does not prejudice novelty.

5.Document D5 discloses the use of an amino acid composition, containing cysteine or cystine as preferred amino acids, in combination with other amino acids, for the treatment of patients with renal diseases, which fall within the definition "acute or chronic kidney diseases" (column 1, lines 5-9; column 2, lines 58-67; examples 1, 2, 4-6; claims). D5 relates to a *combination* of active agents including cysteine or cystine; from column 1, lines 62-64, it is clear that cysteine actively contributes to the treatment (i.e. it is not an excipient). It is to be noted that present claims 1-8 *do not exclude* the presence of other active agents.

What exactly the mechanism is underlying the treatment of renal diseases with cysteine in combination with the other active agents, is not relevant for the assessment of novelty, since the compound used and the disease treated are the same in D5 and in the present application (see also item **V.iii(b)**).

Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1 and 5 is not novel over D5.

6. The subject-matter of the present application can be regarded as a selection invention over D6, which therefore does not prejudice novelty.

7. Document D7 discloses a combination of a leukotriene antagonist and cystine or cysteine to combat inflammatory diseases, such as ischemic renal failure, which falls within the definition "acute or chronic kidney diseases" (par. [0002], [0004], [0009], [0015], [0018], [0042], [0044]-[0045]; claims 1, 29). The administration can be oral, e.g. 140 mg twice a day (par. [0034]). Since cyst(e)ine is a preferred embodiment (see e.g. claim 1), the choice of ischemic renal failure out of a list of diseases cannot be considered as a selection invention.

As in item **V.iii(c)(5)**, the fact that D7 relates to a *combination* of active agents including cysteine or cystine does not render the present claims novel over D5, as they do not exclude the presence of other active agents. Equally, the exact function of cyst(e)ine in the combination with a leukotriene antagonist, is of no relevance for the assessment of novelty, since the compound used and the disease treated are the same in D7 and in the present application (see also item **V.iii(b)**).

Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1 and 5 is not novel over D7.

8. In document D8, the use of a nutritional composition to prevent or treat acute renal failure, which falls within the definition "acute or chronic kidney diseases", is disclosed

(column 1, line 60 - column 2, line 2; column 2, lines 27-30; column 5, line 30 - column 6, line 59; claims 1, 2, 6). Cysteine may be use to prevent injury to the kidney (column 4, lines 31-40). It is to be noted that the dosage of cystine and/or cysteine disclosed in claims 6-8 does not give any indication about the time-frame used; any dosage disclosed in the prior art is therefore novelty-destroying for this feature. Therefore, and in view of items **V.iii(a)** and **V.iii(c)(5)** (combination), the subject-matter of present claims 1, 5 and 7 is not novel over D8.

9. Document D9 discloses an oral amino acid preparation for renal insufficiency, which falls within the definition "acute or chronic kidney diseases", containing cysteine or cystine. Therefore, and in view of items **V.iii(a)** and **V.iii(c)(5)** (combination), the subject-matter of present claims 1 and 5 is not novel over D9.

10. Document D10 discloses oral amino acid mixtures, which may contain cysteine or cystine, for the treatment of acute renal insufficiency or chronic renal insufficiency, with or without dialysis (claims 1, 3, 5, 6; p. 3, lines 1-32; p. 4, line 11 - p. 5, line 25; p. 6, lines 26-30). The composition improves the therapy outcome for patients on dialysis or allows to postpone a dialysis treatment; this implies that it is administered before dialysis (p. 3, lines 9-10).

According to D16, untreated chronic renal failure progresses from moderate to end-stage renal disease (p. 1847, left-hand column, par. 4); therefore, treatment or prevention of chronic renal failure prevents end-stage renal disease.

Therefore, and in view of items **V.iii(a)**, **V.iii(b)**, **V.iii(c)(5)** (combination) and **V.iii(c)(8)** (dosage), the subject-matter of present claims 1, 2, 4 and 5-8 is not novel over D10.

11. Document D11 reports the use of oral L-2-Oxothiazolidine-4-carboxylate (OTZ), a cysteine prodrug, in peritoneal dialysis, a procedure different from the presently claimed haemodialysis. Therefore, D11 is not prejudicial to the novelty of the present claims.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of alternative medicaments for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure or for the treatment or prevention of acute or chronic kidney diseases or end-stage renal disease. The proposed solution is the use of oral cystine and/or cysteine.

(b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 does not involve an inventive step in the sense of Article 33(3)

PCT, as it is also not novel.

(c) As far as the prevention and treatment of acute or chronic kidney diseases, including acute or chronic kidney failure, or the *prevention* of End-stage Renal Disease is concerned (claims 1 (and dependent thereon claim 3) and 7-8), even if novelty could be restored, the present application would very likely lack inventive step over each of D1-D3, D5, D7-D10, which clearly teach the use of oral cysteine or cystine for the claimed diseases.

(c) As far as the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure is concerned (claims 1 (and dependent claim 3), 2, 4 and 6), the following is to be noted: Provided the novelty objection (see item **V.iii(c)(10)**) could be overcome, the subject-matter of these claims may involve an inventive step for the following reasons:

Document D12, which can be considered to represent the closest state of the art, discloses that intravenous administration of N-acetylcysteine decreases the effects of oxidative stress in patients with renal disease undergoing haemodialysis. A study is mentioned wherein the oral administration of N-acetylcysteine for the same purpose was ineffective.

The subject-matter of present claims 1-4 and 6 differs herefrom in that oral cysteine or cystine is used for the same therapeutic purpose.

The problem to be solved by the present application may therefore be regarded as the provision of an alternative cysteine source, offering advantages in terms of cost, ease and safety, for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure (present description, p. 5, lines 4-8).

The solution proposed in claims 1-4 and 6 of the present application may be considered as involving an inventive step for the following reasons:

From document D13, it is known that cysteine has free-radical reducing activity (p. 1, lines 26-30) and that cysteine, cystine or N-acetylcysteine can be used (in a synergistic combination with lipoic (thioctic) acid) for the treatment of conditions caused by oxidative stress (p. 1, lines 3-15; p. 1, line 26 - p. 2, line 1; p. 2, lines 22-34; claims 1, 3, 4, 7).

However, the skilled person would not be incited to replace intravenous N-acetyl cysteine used in D12 by oral cyst(e)ine, for the following reasons:

(I) cysteine is reported to be less stable, more toxic and less soluble than its prodrug N-acetyl cysteine (see D17; p. 2605, left-hand column, par. 1-2, 7), and

(ii) D12 discloses that *oral* N-acetylcysteine is ineffective to decrease the effects of oxidative stress in patients with renal disease undergoing haemodialysis.

Re Item VIII

Certain observations on the international application

Present claims 1, 3 and 5 refer to the treatment of diseases which actually are not well defined. The use of the definitions "acute and chronic kidney diseases" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT.

It is not fully possible to determine the diseases for which protection might legitimately be sought. The only diseases which appear to be clear are the real and defined diseases mentioned in claims 2, 4 and 6-8.

CLAIMS

1. The use of cystine and/or cysteine to prepare oral medicinal products for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure or for the treatment and prevention of acute or chronic kidney diseases or of End-Stage Renal Disease.

2. The use according to claim 1, for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure.

3. Use as claimed in claim 1 or 2, wherein the cystine and/or cysteine is administered in unit doses ranging from 200 to 1000 mg.

4. Use as claimed in claim 1, 2 or 3, wherein the cystine and/or cysteine is administered before and/or after haemodialysis treatment.

5. Pharmaceutical compositions for oral administration for the prevention and treatment of oxidative stress resulting from haemodialysis treatment in patients suffering from chronic kidney failure or for the treatment and prevention of acute or chronic kidney diseases, containing cysteine or cystine as active constituent.

6. A method for the prevention and treatment of oxidative stress resulting from haemodialysis in patients suffering from chronic kidney failure comprising the administration to said patient from 200 to 1000 mg of cystine and/or cysteine orally before and/or after the haemodyalisis treatment..

7. A method for the prevention and treatment of patients suffering from acute or chronic kidney failure comprising the oral administration to said patient from 200 to 1000 mg of cystine and/or cysteine.

8. A method for the prevention and treatment of patients suffering from End-Stage Renal-Disease comprising the oral administration to said patient

from 200 to 1000 mg of cystine and/or cysteine.